INTRAMOLECULAR AMIDATION OF SULFAMATES CATALYZED BY METALLOPORPHYRINS

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FIELD OF THE INVENTION

The invention relates to methods for direct intramolecular amidation of sulfamates affording cyclic sulfamidates. The method represents an example of asymmetric intramolecular amidation of sulfamate esters with high ee (enantiomeric excess) values, (typically 46-87% ee).

BACKGROUND OF THE INVENTION

Cyclic sulfamidates and sulfonamides are useful building blocks for organic synthesis and drug discovery. Major recent pharmaceutical applications include the carbapenem antibiotic L-786,392 **3** and brinzolamide **4** for the treatment of glaucoma (Rosen *et al. Science* (1999), *283*, 703; Dauban *et al. Org. Lett.* (2000), *2*, 2327; Dauban *et al. Tetrahedron Lett.* (2001), *42*, 1037; FIG. 2). Cyclic sulfamidates have also been utilized in the preparation of amino acids (Baldwin *et al. Tetrahedron: Asymmetry* (1990), *1*, 881; Boulton *et al. J. Chem. Soc., Perkin Trans. 1* (1999), 1421; Halcomb *et al. J. Am. Chem. Soc.* (2002), *124*, 2534) and have been shown to serve as useful chiral auxiliaries for organic synthesis (Oppolzer *et al. Tetrahedron Lett.* (1994), *35*, 3509; Ahn *et al. Tetrahedron Lett.* (1998), *39*, 6321; Lin *et al. Tetrahedron* (1999), *55*, 13983).

Pioneering work by Breslow and co-workers in 1983 demonstrated catalytic intramolecular amidation of sulfonamides with either transition metal porphyrin complexes or rhodium acetate as catalysts gave cyclic sulfonamides in good yields (Breslow *et al. J. Am. Chem. Soc.* (1983), *105*, 6728). Recent studies by Du Bois and co-workers reported rhodium acetate to be an efficient catalyst for intramolecular amidation of sulfamate esters, affording the corresponding cyclic sulfamidates in good to high yields (Du Bois *et al. J. Am. Chem. Soc.* (2001), *123*, 6935). However, the challenge still remains to seek more stereoselective catalysts for the synthesis of optically active cyclic sulfamidates. To our knowledge, the asymmetric intramolecular amidation of such substrates using chiral catalysts is not known.

Metalloporphyrin catalyzed intermolecular nitrogen-atom transfer has attracted considerable attention because of their unique relationship to heme-containing enzymes, high stereoselectivity and catalytic turnover (Che *et al. Org. Lett.* (2000), *2*, 2233). Moderate ee values have been obtained for asymmetric aziridination of alkenes and amidation of saturated C-H bonds (Che *et al. Chem. Commun.* (1997), 2373; Che *et al. Chem. Commun.* (1999), 2377; Marchon *et al. Chem. Commun.* (1999), 989; Che *et al. Chem. Eur. J.* (2002), 1563). The successful isolation of bis(tosylimido)ruthenium(VI) porphyrins have provided useful insights into the mechanism of ruthenium porphyrin catalyzed intramolecular nitrogen-atom transfer reactions (Che *et al. J. Am. Chem. Soc.* (1999), *121*, 9120; Che *et al. Chem. Eur. J.* (2002), 1563).

The present invention describes the first intramolecular amidation of sulfamates catalyzed by a metalloporphyrin and asymmetric intramolecular amidation of sulfamidates catalyzed by a transition metal complex supported by a porphyrin

macrocycle. The target cyclic sulfamidates can be easily converted to α- or β-amino alcohols (Du Bois *et al. J. Am. Chem. Soc.* (2001), *123*, 6935), which are important precursors for drug synthesis and for the synthesis of chiral ligands for asymmetric catalysis (Kajiro *et al. Synlett* (1998), 51; Davies *et al. Tetrahedron Lett.* (1996), *37*, 813; Ghosh *et al. J. Am. Chem. Soc.* (1996), *118*, 2527).

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 provides representative examples of metalloporphyrin catalysts capable of catalyzing intramolecular amidation of sulfamates with high efficiency and high diastereo- and enantio-selectivity.

FIG. 2 provides representative examples of drugs containing the cyclic sulfonamide unit.

FIG. 3 illustrates the described method which involves the direct intramolecular amidation of sulfamates using metalloporphyrins as general and efficient catalysts.

FIG. 4 provides representative examples of intramolecular amidation of sulfamates catalyzed by an electron-deficient ruthenium porphyrin to give the corresponding cyclic sulfamidates in good to excellent yields and excellent diastereoselectivity.

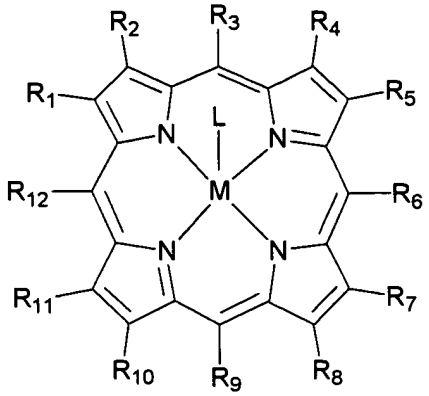
FIG. 5 provides representative examples of intramolecular amidation of sulfamates catalyzed by an electron-deficient ruthenium porphyrin with high turnover numbers.

FIG. 6 provides representative examples of asymmetric intramolecular amidation of sulfamates catalyzed by a chiral ruthenium porphyrin with high enantioselectivity.

FIG 7. provides representative examples of pharmaceutical applications of α-amino alcohols.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides an intramolecular amidation process using a non-chiral metalloporphyrin catalyst and a chiral metalloporphyrin catalyst represented by structural formula:



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wherein

each R_1-R_{12} is independently H, optionally substituted hydroxyl, optionally substituted amino, halogen, -CN, -NO_2, optionally substituted C_{1-20} alkyl, optionally substituted phenyl; optionally substituted naphthyl; optionally substituted anthracenyl, -SR^{13}, -SO_2R^{13}, -CO_2R^{13}, and optionally substituted heteroatom-containing aromatic ring, in which the optional substitutents are independently selected from the foregoing alkyl, phenyl, naphthyl, anthracenyl and heteroatom-containing aromatic groups; R^{13} is independently selected from the same groups as R^1 other than –SR^{13} and –SO_2R^{13}; and L is CO or R^1. The various R groups may be optically pure or can be stereo- and regioisomers.

In an embodiment of this invention, the metalloporphyrin is a transition metal porphyrin, such as ruthenium, manganese, iron, osmium, copper or cobalt porphyrin. In an embodiment of this invention, the porphyrin ligand is a tetraphenylporphyrin and the

phenyl rings are attached at the *meso*-positions of the porphyrin. In an embodiment of the present invention, the catalysts are capable of exhibiting both regio- and stereo-selectivity. Two of the preferred catalysts are shown in Fig. 1. In an embodiment of the present invention, the catalyst is capable of selectively catalyzing intramolecular amidation of saturated C-H bonds. In an embodiment of the present invention, the catalyst is capable of catalyzing asymmetric intramolecular amidation of saturated C-H bonds. In an embodiment of this invention, the stereoselectivity is the formation of only *cis*-configuration cyclic sulfamidates.

Additionally, the present invention provides a method for the preparation of cyclic sulfamidates with the catalysts from sulfamates as starting materials. Further, the present invention provides a method for producing *cis*-cyclic sulfamidates with the catalyst. The present invention also provides a method for producing optically active cyclic sulfamidates with the catalyst. Preferably, the method involves the use of an oxidant which selectively alters the oxidation state of the substrate, preferably in the presence of a solvent and preferably in the the presence of a base. The solvent can be MeOH, MeCN, DMF, $C_4H_4Cl_2$, CH_2Cl_2, and benzene. Typical oxidants include $PhI(OAc)_2$, PhIO and NBS (N-bromosuccinimide). Bases, which scavenge by-products, include Al_2O_3, MgO, ZnO, K_2CO_3 and NaOH. In an embodiment of this invention, the substrate is a sulfamate, a sulfamate derivative, or a hydrocarbon containing a sulfonylamide functional group. As shown in the figures, carbon to which the sulfonylamide moiety is attached can be a part of a cyclic or non-cyclic moiety, which in turn can be substituted with a functional group such as $-CO_2Me$ or by an aromatic or cycloaliphatic group.

As used herein, the term, "stereoselective" refers to selection of an optical isomer. "Enantioselectivity" represents the maximal asymmetric induction and minimal racemization of the optically active products. The term "turnover" refers to the relative number of molecules of products per number of molecules of catalyst prior to the exhaustion of a given reaction.

EXAMPLES

EXAMPLE 1

Intramolecular Amidation of Sulfamate Esters Catalyzed by Electron-Deficient Ruthenium Porphyrin **1**

The invention relates to a direct method for the synthesis of cyclic sulfamidates using ruthenium porphyrin **1** (prepared according to: Murahashi *et al. Tetrahedron Lett.* (1995), *36*, 8059; Groves *et al. J. Am. Chem. Soc.* (1996), *118*, 8961) as a general and effective catalyst for the direct intramolecular amidation of sulfamates.

Typical conditions employ 1.5 mol% of **1**, 1 equiv. of sulfamate ester, 2 equiv. of $PhI(OAc)_2$, 2.5 equiv. of anhydrous Al_2O_3 (pH = 7-7.4) in CH_2Cl_2 (distilled from CaH_2 prior to use) under argon at 40 °C for 2 h. Commercially available Al_2O_3 was dried to a constant weight at 250°C for 12 h. The reaction mixture was cooled to 25°C, diluted with 5 mL of CH_2Cl_2, and filtered through a pad of Celite®. The filter cake was rinsed with 2 × 5 mL of CH_2Cl_2 and the combined filtrates were evaporated under reduced pressure. The residue was purified by silica gel chromatography (Merck, 230-400 mesh) to afford the corresponding cyclic sulfamidates. AcOH generated as a by-product from $PhI(OAc)_2$ was scavenged from the reaction mixture by addition of base. Following a series of control

experiments, Al_2O_3 proved to be the best among MgO, ZnO, K_2CO_3, Al_2O_3 and NaOH, in that it gave the highest product yields.

With only 1.5 mol% catalyst loading, sulfamates **5-10** were converted to the corresponding cyclic sulfamidates **11-16** in good to high yields (see FIG. **4**). The highest yield (88%) was achieved for the intramolecular amidations of **7** and **10**. Catalyst **1** shows high catalytic efficiency and excellent *cis*-selectivity. For substrates **7**, **8** and **10**, only *cis*-cyclic sulfamidates **12**, **13** and **16** were obtained, respectively. The *trans*-cyclic sulfamidates were undetected. This shows that ruthenium porphyrin **1** has better stereoselectivity than rhodium acetate (a 8:1 mixture of *cis* and *trans* isomers was obtained for the reaction of **8** catalyzed by rhodium acetate. See: Du Bois *et al. J. Am. Chem. Soc.* (2001), *123*, 6935). The oxidant used in the catalytic reaction is $PhI(OAc)_2$, which is commercially available. For substrates **5-7,** and **10**, six- rather than five-membered ring heterocycles **11-13** and **16** were formed in high yields (76-88%). For substrates **8** and **9**, five-membered ring formation gave cycloadducts **14** and **15** in moderate yields of 61 and 56%, respectively.

All the target cyclic sulfamidates were characterized by ^1H, ^{13}C and NOESY NMR spectroscopy and HRMS spectrometry. The spectral data of **11-14** are identical with those reported in the literature (see: Du Bois *et al. J. Am. Chem. Soc.* (2001), *123*, 6935). **9:** ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.29 (m, 5H), 4.82 (s, 2H), 4.37 (t, J = 9.3 Hz, 2H), 3.03 (t, J = 9.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 136.4, 128.9, 128.7, 127.0, 71.4, 35.2; HRMS (EI) calcd. for $C_8H_{11}NO_3S$: 201.0460, found: 201.0456. **10**: ^1H NMR ($CDCl_3$, 400 MHz) 7.23 (m, 5H), 4.66 (s, 2H), 4.34 (m, 1H), 3.15 (dd, 1H, J = 13.6 Hz), 2.32 (m, 2H), 1.10-1.86 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) 140.0, 129.2, 128.3,

126.0, 87.2, 44.0, 38.9, 32.4, 30.0, 24.5, 24.4; HRMS (EI) calcd. for $C_{13}H_{19}NO_3S$: 269.1087, found: 269.1090. **15**: ^{1}H NMR ($CDCl_3$, 400 MHz) 7.43 (m, 5H), 5.07 (m, 1H), 4.84 (m, 2H), 4.45 (t, J = 6.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 135.3, 129.5, 129.4, 126.7, 75.0, 59.6; HRMS (EI) calcd. for $C_8H_9NSO_3$: 199.0303, found: 199.0297. **16**: ^{1}H NMR ($CDCl_3$, 400 MHz) 7.37 (m, 5H), 4.60 (m, 1H), 4.39 (m, 2H), 2.14 (m, 1H), 1.10-1.85 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) 136.7, 129.3, 129.1, 127.3, 86.9, 64.3, 45.3, 31.8, 29.7, 24.8, 24.4; HRMS (EI) calcd. for $C_{13}H_{17}NO_3S$: 267.0929, found: 267.0935.

EXAMPLE 2

Turnover number refers to the relative number of molecules of product per number of molecules of catalyst prior to the exhaustion of a given reaction and shows a very important aspect of catalyst efficiency. The turnover numbers for the analogous rhodium acetate catalyzed reactions do not exceed 50 (see: Du Bois *et al. J. Am. Chem. Soc.* (2001), *123*, 6935). With electron-deficient ruthenium porphyrin **1** as catalyst, intramolecular amidation of **5** and **7** afforded turnover numbers of 290 and 301, respectively (FIG. 5). This shows that **1** is more robust catalyst than rhodium (II,II) dimmer complexes (the reaction conditions are almost the same as those for EXAMPLE 1, and with a lower catalyst loading in EXAMPLE 2. See FIG. 5 footnote).

EXAMPLE 3

Asymmetric Intramolecular Amidation of Sulfamate Ester Catalyzed by Chiral Ruthenium Porphyrin **2**

With chiral ruthenium porphyrin **2** as catalyst (prepared according to: Che *et al. Chem. Commun.* (1997), 1205), sulfamates **5**, **8** and **9** undergo enantioselective C-H insertion to

give the corresponding cyclic sulfamidates with high ee values (typically 46-87%, FIG. 6). As shown in FIG. 6, an ee (enantiomeric excess) of 46% or more can be achieved. In order to reduce the amount of by-products, the substrate to $PhI(OAc)_2$ ratio was decreased from 2 to 1.4. Solvent has a very important effect on ee values obtained. For example, reaction of sulfamate ester **5** in CH_2Cl_2 gave **11** with 46% ee (entry 1). In comparison, the analogous reaction carried in C_6H_6 gave **11** with an ee value of 79% (entry 2). Similar outcomes were obtained for substrates **8** and **9**.

Similarly, reaction temperature has an effect on the ee values. With benzene as solvent, lowering the reaction temperature to 4°C resulted in an increase in ee values (entries 2 and 3: from 79 to 84%; entries 5 and 6: from 82 to 87%; entries 8 and 9: from 81 to 82%).

The present invention provides an efficient method for the synthesis of chiral cyclic sulfamidates. These compounds are useful synthetic intermediates in the preparation of optically active α- or β-amino alcohols of biological importance. For example, optically active **17** is currently receiving considerable attention as a key component of the HIV protease inhibitor Indinavir **18** (see: Hiyama *et al. Synlett* (1998), 51. FIG. 7). Amino alcohol **17** can be prepared from (1*S*,2*R*)-**14** upon hydrolysis (see: Du Bois *et al. J. Am. Chem. Soc.* (2001), *123*, 6935). Using commercially available achiral 2-indanol, amino alcohol **17** can be obtained in 3 steps; optically active **17** requires 8 steps from the chiral amino acid (see: Hiyama *et al. Synlett* (1998), 51).